



NDA 204096/S-005

SUPPLEMENT APPROVAL

Astellas Pharma US, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Pritza:

Please refer to your Supplemental New Drug Application (sNDA) dated November 1, 2017, received November 1, 2017, and your amendments, including the major amendment submitted on August 8, 2018, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ASTAGRAF XL® (tacrolimus extended-release capsules).

This Prior Approval supplemental new drug application, as amended, provides for submission of pediatric clinical studies PMR-EC-1206 and PMC-EC-1207 in pediatric transplant patients, including pediatric kidney transplant patients. The information from these studies supports revision of ASTAGRAF XL labeling to include pharmacokinetic data in pediatric kidney transplant patients, as well as long-term safety and clinical outcome data.

This supplement application also includes the addition of the adverse reaction, calcineurin-inhibitor induced pain syndrome, to Section 6.2 of the labeling and provides updated labeling in Sections 8.1, 8.2, and 8.3 to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

This final version of the labeling includes two minor edits:

- in Highlights of Prescribing Information, under **RECENT MAJOR CHANGES**, the revision date "11/2018" was added as follows:

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2018
Dosage and Administration (Pediatric Initial Dosage) (2.2)	11/2018

- In section **6 ADVERSE REACTIONS** the bolding of the characters of the first sentence was removed to show as follows:
"The following clinically significant adverse drug reactions are discussed in greater detail in other sections of labeling"

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effectuated" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated November 1, 2017, containing the final report for the following postmarketing requirement, listed in the July 19, 2013 approval letter:

- 2061-2 PMR-EC-1206, Phase 2, Open Label, Multicenter Study to Compare Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted from Prograf® Based Immunosuppressive Regimen to Tacrolimus

Prolonged Release, Advagraf® Based Immunosuppressive Regimen, including a Long-Term Follow-up

Final Protocol Submission: Completed
Study Completion: 12/2016
Final Report Submission: 12/2017

We have reviewed your submission and conclude that the above requirement was fulfilled.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We note that you have fulfilled the pediatric study requirements for all relevant pediatric age groups for this application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and prescribing information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RENATA ALBRECHT
11/29/2018